SCIENTIFIC COUNCIL OF MEDICINE
UNIVERSITY OF BELGRADE

At the meeting of the Scientific Council of the Faculty of Medicine in Belgrade, held on 25.12.2014. No. 4600/12, the Evaluation Board for the assessment of the completed PhD thesis entitled:

‘’Interventions for primary biliary cirrhosis and osteoporosis in patients with primary biliary cirrhosis: Cochrane reviews with meta-analyses and trial sequential analyses of randomized clinical trials’’

written by candidate Dr Jelena Rudić, Clinical Teaching Assistant at the Chair of Internal Medicine, Faculty of Medicine, University of Belgrade, was appointed. The tutor of the PhD. thesis is Prof. Dr. Miodrag Krstić and co-tutor, Prof. Dr. Christian Gluud, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

The members of the appointed Evaluation Board are:

1. Prof. Dr. Tatjana Pekmezović, Faculty of Medicine, University of Belgrade,
2. Prof. Dr. Đorđe Ćulafić, Faculty of Medicine, University of Belgrade,
3. Prof. Dr. Goran Bjelaković, Faculty of Medicine, University of Niš,

Based on the analysis of the submitted PhD thesis, the Evaluation Board submits to the Scientific Council of Medical Faculty the following

REPORT

A) The contents of the thesis

PhD thesis of candidate Rudić Jelena is written on 299 pages and is divided into the following sections: Introduction, Objectives, Materials and Methods, Results, Discussion, Conclusions and References. The thesis contains a total of 117 images and 37 tables. Doctoral dissertation contains a Summary in Serbian and English, the Candidate's biography, and information about the Board.

In the Introduction, the novel perspectives on the pathogenesis of primary biliary cirrhosis are described, as well as the current consensus on diagnosis and management of primary biliary cirrhosis. Over the last few years there have been improvements in the treatment of primary biliary cirrhosis which was addressed in detail in the introduction part. Problems facing hepatologists and patients in the treatment of primary biliary cirrhosis and its frequent complication – osteoporosis were discussed. In the text, a brief review of different treatment options for osteoporosis associated with primary biliary cirrhosis was given, and pathogenesis of osteoporosis in primary biliary cirrhosis was described.

The objectives of the thesis are clearly defined. The objective of this doctoral thesis was to summarize the evidence from Cochrane systematic reviews on treatment options for patients with primary biliary cirrhosis and osteoporosis associated with primary biliary cirrhosis. The objectives of Cochrane systematic reviews included in the thesis were to assess the beneficial and harmful effects of different interventions in patients with primary biliary cirrhosis and osteoporosis associated with primary biliary cirrhosis.

In the Materials and Methods section it is noted that the thesis is consisted of systematic reviews of all relevant randomized clinical trials regarding primary biliary cirrhosis and osteoporosis associated with primary biliary cirrhosis. Types of participants, interventions and outcome measures were described in detail for each systematic review included in the thesis. Meta-analyses and trial sequential analysis were performed to quantify the estimated effect of various interventions using The Cochrane Collaboration methodology. All systematic reviews were performed according to protocols published in the Cochrane Database of Systematic Reviews. Included trials were identified through The Cochrane Library, Medline, Embase, and Science Citation Index Expanded. Data extraction and the assessment of risk of bias were conducted by two authors independently of each other. Continuous data were analyzed using mean difference (MD) and standardized mean difference (SMD). Dichotomous data were analyzed using risk ratio (RR). Meta-analyses were conducted using both a random-effects model and a fixed-effect model, with 95% confidence intervals (CI). Trial sequential analysis was used to assess risk of random errors (play of chance). Risks of bias (systematic error) in the included trials were assessed according to Cochrane methodology bias domains.

In the Results section, all the results are presented clearly and in detail.

The discussion is written clearly and transparently, with comparative examination of the results of the doctoral dissertation with the data in other studies (references).

The Conclusions summarize the most important findings that have emerged from the results of the thesis. The Bibliography contains a list of 283 references.

B) A brief description of the results achieved

The four Cochrane systematic reviews were included in the thesis with a total of 30 trials with 1,847 participants. In the ursodeoxycholic acid review 16 randomized clinical trials with 1447 patients with primary biliary cirrhosis were included, out of which 14 trials compared ursodeoxycholic acid with placebo and 2 trials compared ursodeoxycholic acid with no intervention. Ursodeoxycholic acid versus placebo or no intervention did not significantly affect all-cause mortality, all-cause mortality or liver transplantation, adverse events, liver transplantation, pruritus, fatigue, or liver-related morbidity in patients with primary biliary cirrhosis. Ursodeoxycholic acid seemed to have a beneficial effect on liver biochemistry measures and on histological progression compared with placebo or no intervention. In the bezafibrate review 6 randomized clinical trials with 151 Japanese patients with primary biliary cirrhosis were included, out of which 4 trials compared bezafibrate versus no intervention, and 2 trials compared bezafibrate with ursodeoxycholic acid. Bezafibrate did not demonstrate any significant effect on mortality, liver-related morbidity, or adverse events when compared with no intervention, or when compared with ursodeoxycholic acid. Bezafibrate did not demonstrate any significant effect on pruritus compared with no intervention. The results of trial sequential analysis imply that there is firm evidence for a beneficial effect of bezafibrate on decreasing the activity of serum alkaline phosphatases when compared with no intervention, or when compared with ursodeoxycholic acid. All the other biochemical markers assessed showed non-significant effect estimates. In the bisphosphonates review 6 randomized clinical trials with 200 participants with primary biliary cirrhosis having osteoporosis were included, out of which 3 trials with 106 participants compared etidronate or alendronate with placebo or no intervention; 2 trials with 62 participants compared etidronate or alendronate with alendronate or ibandronate; and 1 trial with 32 participants compared etidronate with sodium fluoride. Statistical analyses found no evidence

of effect of any of the aforementioned three bisphosphonates on mortality, fractures, adverse events, liver-related mortality, liver transplantation, liver-related morbidity or bone mineral density measured by dual-energy X-ray absorptiometry in patients with primary biliary cirrhosis. The results of trial sequential analysis imply that there is firm evidence for a beneficial effect of bisphosphonates on decreasing urinary amino telopeptides of collagen I (NT_x) concentration compared with placebo or no intervention. Etidronate compared with sodium fluoride significantly decreased serum osteocalcin, urinary hydroxyproline, and parathyroid hormone concentration. All the other biochemical markers of bone turnover assessed showed non-significant effect estimates. In the hormone replacement review 2 randomised clinical trials with 49 participants were included, which compared the effect of hormone replacement on treatment of osteoporosis in women with primary biliary cirrhosis with placebo or no intervention. Statistical analyses found no significant effect of hormone replacement on mortality, fractures, lumbar spine bone mineral density measured by dual-energy X-ray absorptiometry, liver-related mortality, liver transplantation, or liver-related morbidity in women with primary biliary cirrhosis. Hormone replacement significantly increased adverse events and number of patients having hormone replacement withdrawn due to adverse events. Hormone replacement may decrease bone mineral density at the proximal femur.

C) Comparative analysis of the doctoral thesis with the results from the literature

In consistency with previous meta-analyses and reviews, an updated systematic review assessing the effects of ursodeoxycholic acid in patients with primary biliary cirrhosis did not demonstrate any benefit of ursodeoxycholic acid on all-cause mortality, and all-cause mortality or liver transplantation in these patients. This observation is in contrast to some previous attempts to aggregate data from studies assessing ursodeoxycholic acid interventions for primary biliary cirrhosis. Regarding other reviews included in the thesis, it was not possible to compare results with the results from other systematic reviews or meta-analysis, as it was not possible to identify any meta-analyses or systematic reviews assessing bezafibrate in primary biliary cirrhosis, nor bisphosphonates or hormone replacement for osteoporosis in people with primary biliary cirrhosis that have summarised the evidence in a systematic way. Cochrane systematic reviews have demonstrated that bisphosphonates have statistically significant and clinically important benefit in the secondary prevention of vertebral, non-vertebral, and hip fractures in

postmenopausal women. There is evidence that hormone replacement increases bone mineral density and reduces the incidence of vertebral and non-vertebral fractures in postmenopausal women. One could argue that patients with primary biliary cirrhosis plus osteoporosis should be treated as women without primary biliary cirrhosis having osteoporosis. This may turn out to be correct. However, according to the results from present review it is impossible to conclude if this is so.

D) The published papers resulting from the thesis

1. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Ursodeoxycholic acid for primary biliary cirrhosis. Cochrane Database Syst Rev 2012; 12:CD000551. doi: 10.1002/14651858. **M21 IF 5.785**
2. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Bezafibrate for primary biliary cirrhosis. Cochrane Database Syst Rev 2012; 1:CD009145. doi: 10.1002/14651858. **M21 IF 5.785**
3. Rudic JS, Giljaca V, Krstic MN, Bjelakovic G, Gluud C. Bisphosphonates for osteoporosis in primary biliary cirrhosis. Cochrane Database Syst Rev 2011; 12:CD009144. doi: 10.1002/14651858. **M21 IF 5.912**
4. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Hormone replacement for osteoporosis in women with primary biliary cirrhosis. Cochrane Database Syst Rev 2011; 12:CD009146. doi: 10.1002/14651858. **M21 IF 5.912**

E) Conclusion (explanation of scientific contribution)

The PhD thesis **‘’Interventions for primary biliary cirrhosis and osteoporosis in patients with primary biliary cirrhosis: Cochrane reviews with meta-analyses and trial sequential analyses of randomized clinical trials’’** by the PhD candidate Jelena Rudić, is an original scientific contribution in the field of hepatology. The results of this doctoral thesis provide the best available evidence for the treatment of primary biliary cirrhosis and osteoporosis associated with primary biliary cirrhosis, and may be useful in further clinical practice and health-care decision making. The thesis assess and summarizes benefits and harms of clinical

interventions in primary biliary cirrhosis, and facilitates implementation of evidence-based medical interventions into clinical practice. Furthermore, the results of thesis also reveal lack of evidence, and define the specific need for future randomized clinical trials.

The work on this PhD thesis is done according to the principles of scientific research. The objectives are clearly defined, scientific approach was original and carefully chosen, and a working methodology was contemporary. The results are clearly and systematically presented and discussed, and from them the appropriate conclusions are derived.

Based on all abovementioned, and in view of the current research work of the candidate, the Board proposes to the Scientific Council, Faculty of Medicine, University of Belgrade to accept the PhD thesis of the candidate Dr Jelena Rudić, and approve its public defense, in order to acquire the academic title of doctor (PhD) of medical sciences (area - epidemiology).

Belgrade, 20.02.2015.

Mentor:

Prof. dr Miodrag Krstić

_____

Co-mentor:

Prof. dr Christian Gluud

_____

Members of the Board:

Prof. dr Tatjana Pekmezović

_____

Prof. dr Đorđe Ćulafić

_____

Prof. dr Goran Bjelaković

_____